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(71) Applicant: CEPHALON, INC. [US/US]; 145 Brandywine Parkway, West Chester, PA 19380 (US).

(72) Inventors: MALLAMO, John, P.; 616 Font Road, Glenmore, PA 19343 (US). BIHOVSKY, Ron; 804 Primrose Lane, Wynnewood, PA 19096 (US). TAO, Ming; 1604 Squire Drive, Maple Glen, PA 19002 (US). WELLS, Gregory, J.; 818 Serpentine Drive, West Chester, PA 19382 (US).

(74) Agents: MILLER, Suzanne, E. et al.; Woodcock Washburn Kurtz Mackiewicz & Norris, 46th floor, One Liberty Place, Philadelphia, PA 19103 (US).

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(54) Title: PHOSPHOROUS-CONTAINING CYSTEINE AND SERINE PROTEASE INHIBITORS

(57) Abstract

The present invention is directed to novel phosphorous-containing inhibitors of cysteine or serine prooteases. Methods for the use of the protease inhibitors are also described.

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PHOSPHOROUS-CONTAINING CYSTEINE AND SERINE PROTEASEE INHIBITORS

CROSS REFERENCE TO RELATED APPLICATIONSS

This application claims benefit of U.S. Provisional Application Serial No. 60/001,491, filed July 17, 1995.

FIELD OF THE INVENTION

Novel inhibitors of cysteine or serine pproteases, referred to herein as β-keto phosphates, β-keto phosphinates, β-keto phosphonates, α-keto phosphonates, α-keto phosphinates, and α-keto phosphine oxides, methodss for making these novel compounds, and methods for usinng the same are disclosed.

BACKGROUND OF THE INVENTION

Numerous cysteine and serine proteases hhave been identified in human tissues. A "protease" is an eenzyme which degrades proteins into smaller components (ppeptides). The terms "cysteine protease" and "serine proteasee" refer to proteases which are distinguished by the presence therein of a cysteine or serine residue which plays a criticaal role in the catalytic process. Mammalian systems, includiing humans,

normally degrade and process proteins via a varieety of enzymes including cysteine and serine proteases. However, when present at elevated levels or when abnormallly activated, cysteine and serine proteases may be iinvolved in pathophysiological processes.

For example, calcium-activated neutral proteases ("calpains") comprise a family of intracellular ccysteine proteases which are ubiquitously expressed in mammmalian tissues. Two major calpains have been identifiedd; calpain I and calpain II. While calpain II is the predomimnant form in many tissues, calpain I is thought to be the preddominant form in pathological conditions of nerve tissues.. The calpain family of cysteine proteases has been impplicated in many diseases and disorders, including neurodegemneration, stroke, Alzheimer's, amyotrophy, motor neuron dammage, acute central nervous system injury, muscular dystrophyy, bone resorption, platelet aggregation, cataracts and inflammation. Calpain I has been implicated in eexcitatory amino-acid induced neurotoxicity disorders includding ischemia, hypoglycemia, Huntington's Disease, andd epilepsy. The lysosomal cysteine protease cathepsin B has bbeen implicated in the following disorders: arthritis,, inflammation, myocardial infarction, tumor metasttasis, and muscular dystrophy. Other lysosomal cysteine prooteases include cathepsins C, H, L and S. Interleukin-1ßß converting enzyme ("ICE") is a cysteine protease which catallyzes the formation of interleukin-1ß. Interleukin-1ß is aan immunoregulatory protein implicated in the followwing disorders: inflammation, diabetes, septic shock, rheumatoid arthritis, and Alzheimer's disease. ICE has alsoo been linked to apoptotic cell death of neurons, which is implicated in a variety of neurodegenerative disoorders including Parkinson's disease, ischemia, and amyootrophic lateral sclerosis (ALS).

Specific β-keto phosphinates have been described as inhibitors of ICE, cathepsin B, and calpain ((R. E. Dolle, et al., J. Med. Chem. 1995 38, 220-222). *See allso* European Patent Application Pub. No. 0 644 197 A1.

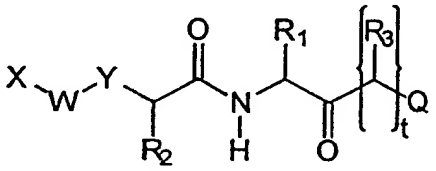
Cysteine proteases are also produced bpy various pathogens. The cysteine protease clostripain iss produced by Clostridium histolyticum. Other proteases are pproduced by Trpanosoma cruzi, malaria parasites Plasmodium ffalciparum and P.vinckei and Streptococcus. Hepatitis A viiral protease HAV C3 is a cysteine protease essential for proccessing of picornavirus structural proteins and enzymes.

Exemplary serine proteases implicated in degenerative disorders include thrombin, human lleukocyte elastase, pancreatic elastase, chymase and catheppsin G. Specifically, thrombin is produced in the blood coagulation cascade, cleaves fibrinogen to form fibrin and aactivates Factor VIII; thrombin is implicated in thrombophlebitis, thrombosis and asthma. Human leukocyte elastasee is implicated in tissue degenerative disorders suchh as rheumatoid arthritis, osteoarthritis, atherosclerosis, bronchitis, cystic fibrosis, and emphysema. Pancreatic elastase is implicated in pancreatitis. Chymasee, an enzyme important in angiotensin synthesis, is implicateed in hypertension, myocardial infarction, and coronarry heart disease. Cathepsin G is implicated in abnormal connective tissue degradation, particularly in the lung.

Given the link between cysteine and seerine proteases and various debilitating disorders, compounds which inhibit these proteases would be useful anad would provide an advance in both research and clinicall medicine. The present invention is directed to these, as wwell as other, important ends.

SUMMARY OF THE INVENTION

The present invention is directed to novel cysteine and serine protease inhibitors referreed to herein as β-keto phosphates, β-keto phosphinates, β-ketto phosphonates, α-keto phosphonates, α-keto phospphinates, and α-keto phosphine oxides. These novel compoundss are represented by the following Formula I:



I

wherein:

X is aryl having from about 6 to about 14 carbons, heteroaryl having from about 6 to about 14 ringg atoms, aralkyl having from about 7 to about 15 carbonss, alkyl having from 1 to about 10 carbons, said alkyl ggroups being optionally substituted with one or more J groupss, heteroalkyl having from 2 to about 7 carbons, aalkoxy having from 1 to about 10 carbons, aralkyloxy having ffrom about 7 to about 15 carbons, or a carbohydrate moiety opptionally containing one or more alkylated hydroxyl groupss;

W is carbonyl or SO_2;

Y is NH or $(CH_2)_k$ where k is an integer froom 0 to 3;

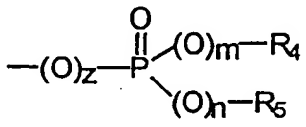
R_1 and R_2 are independently hydrogen, alkyll having from one to about 14 carbons, or cycloalkyl having ffrom 3 to about 10 carbons, said alkyl and cycloalkyl groups being optionally substituted with one or more J groupss;

R_3 is hydrogen, lower alkyl, aryl, heteroarryl, aralkyl, or heteroaralkyl;

t is 0 or 1;

J is halogen, alkyl, aryl, heteroaryl, amino optionally substituted with one to three aryl or lower alkyl groups, guanidino, alkoxycarbonyl, alkoxy, hydroxy, aryloxy, aralkyloxy, heteroalkyl, or carboxy; and

Q has the formula



wherein:

m, n, and z are each independently 0 or 1;

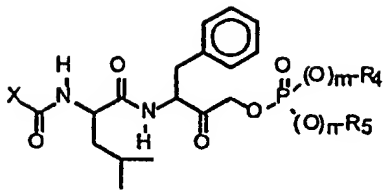
R_4 and R_5 are each independently hydrogen, lower alkyl optionally substituted with J, aryl optionally substituted with J, aralkyl optionally substituted with J, or heteroaryl optionally substituted with J;

or R_4 and R_5 may be taken together along with the $-(O)_m-P(=O)-(O)_n-$ of Q to form a 5-8 membered heterocyclic ring, optionally substituted with J;

or R_4 and R_5 taken together may form an aralkyl group;

with the proviso that when t is 0, z is also 0; and with the proviso that when m and n are both 0, and t and z are both 1, R_4 and R_5 cannot be unsubstituted phenyl or halogen-substituted phenyl; and with the further proviso that R_1 cannot be methylene substituted with a carboxyl group.

Some preferred embodiments of the compounds of Formula I are represented by compounds having the Formulla Ia:



Ia

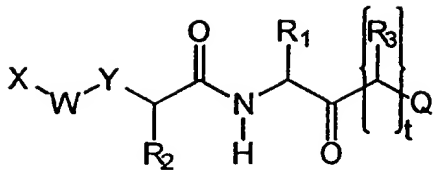
wherein X, R_4, R_5, m and n are as previously defiined.

The compounds of the invention are useful ffor the irreversible inhibition of cysteine and serine pproteases. Beneficially, these compounds find utility in a variety of settings. For example, in the research arena, tthe claimed compounds can be used, for example, in discoveryy of agents for treating disorders associated with abnormal and/or aberrant activity of cysteine and/or serine protteases. In a clinical arena, for example, the compounds can bbe used to alleviate, mediate, reduce, and/or prevent disorrders which are associated with abnormal and/or aberrant acttivity of cysteine and/or serine proteases. Methodologiess for making our β-keto phosphates, β-keto phosphinates, β-ketto phosphonates, α-keto phosphonates, α-keto phosphhinates, and α-keto phosphine oxides are also disclosed.

These and other features of the compounds oof the subject invention are set forth in more detail bbelow.

DETAILED DESCRIPTION

Novel cysteine and serine protease inhibitoors have been discovered which are represented by the general Formula I:



I

wherein:

X is aryl having from about 6 to about 14 carbons, heteroaryl having from about 6 to about 14 ring atoms, aralkyl having from about 7 to about 15 carbons,, alkyl having from 1 to about 10 carbons, said alkyl groups being optionally substituted with one or more J groups, heteroalkyl having from 2 to about 7 carbons, alkoxy having from 1 to about 10 carbons, aralkyloxy having from about 7 to about 15 carbons, or a carbohydrate moiety optionally containing one or more alkylated hydroxyl groups;

W is carbonyl or SO_2;

Y is NH or $(CH_2)_k$ where k is an integer from 0 to 3;

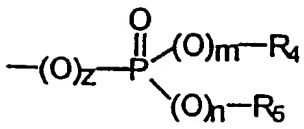
R_1 and R_2 are independently hydrogen, alkyl having from one to about 14 carbons, or cycloalkyl having from 3 to about 10 carbons, said alkyl and cycloalkyl groups being optionally substituted with one or more J groups;

R_3 is hydrogen, lower alkyl, aryl, heteroaryl, aralkyl, or heteroaralkyl;

t is 0 or 1;

J is halogen, alkyl, aryl, heteroaryl, amino optionally substituted with one to three aryl or lower alkyl groups, guanidino, alkoxycarbonyl, alkoxy, hydroxy, aryloxy, aralkyloxy, heteroalkyl, or carboxy; and

Q has the formula:



wherein:

m, n, and z are each independently 0 or 1;

R_4 and R_5 are each independently hydrogen, lower alkyl optionally substituted with J, aryl optionally substituted with J, aralkyl optionally substituted with J, or heteroaryl optionally substituted with J;

or R_4 and R_5 may be taken together along with the $-(O)_m-P(=O)-(O)_n-$ of Q to form a 5-8 membered heterocyclic ring optionally substituted with J;

or R_4 and R_5 taken together may form an aralkyl group;

with the proviso that when t is 0, z is also 0; and with the proviso that when m and n are both 0, and t and z are both 1, R_4 and R_5 cannot be unsubstituted phenyl or halogen-substituted phenyl; and with the further proviso that R_1 cannot be methylene substituted with a carboxyl group.

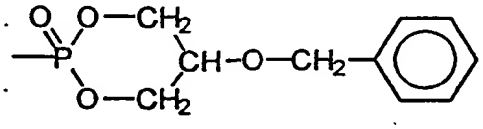
In some preferred embodiments R_1 is aralkyl. In other preferred embodiments R_2 is alkyl. In further preferred embodiments R_3 is hydrogen. Preferably, Y is NH.

Also, in some preferred embodiments X is alkoxy, aralkyloxy, a carbohydrate moiety or, together with W, heteroalkylsulfonyl. In particularly preferred embodiments X is benzyloxy or *t*-butoxy.

In some preferred embodiments m and n are 1, and R_4 and R_5 are independently hydrogen, lower alkyl optionally substituted with J where J is preferably alkyl or aryl, aryl substituted with J where J is preferably halogen or alkyl,

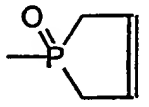
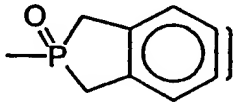
aralkyl optionally substituted with J where J iss preferably alkyl or aryloxy, or R_4 and R_5 taken together with the $-(O)_m-P(=O)-(O)_n-$ of Q form a six membered ring tthat is substituted by J.

In particularly preferred embodiments R_4 anad R_5 are independently H, methyl, butyl, 2-ethylhexyl, 2--cyclohexylethyl, 2-phenylethyl, 4-chlorophenyl, benzyl, 2-methylbenzyl, and 3-phenoxybenzyl, or R_4 and R_5, taken together with the the $-(O)_m-P(=O)-(O)_n-$ of Q formm a six-membered ring having the formula:



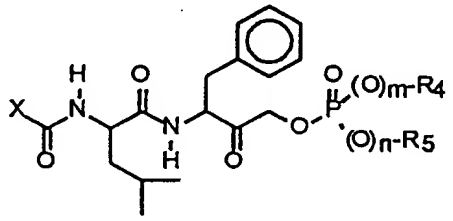
In other preferred embodiments m and n are 0, and R_4 and R_5 are independently aralkyl, lower alkyl optionally substituted with J where J is preferably alkyl, aryl or heteroalkyl, aryl optionally substituted with J where J is alkyl or alkoxy, or R_4 and R_5 taken together with the $-(O)_m-P(=O)-(O)_n-$ of Q form a five membered ring.

In particularly preferred embodiments wheree m and n are 0, R_4 and R_5 are independently methyl, ethyl, penntyl, 2-phenylethyl, phenyl, 2-methylphenyl, 2-methoxyphhenyl, 3-methoxyphenyl, 4-methoxyphenyl, and 3-morpholincopropyl, or R_4 and R_5 taken together with the $-(O)_m-P(=O)-(O)_n-$ of Q form a five-membered ring having the formula:

 or the formula 

In further preferred embodiments m is 1, n is 0, and R_4 and R_5 are independently aryl, aralkyl, or lower alkyl optionally substituted with J where J is heteroalkyl. In particularly preferred embodiments where m is 1 and n is 0, R_4 and R_5 are methyl, ethyl, benzyl, phenyl, 2-morpholinoethyl, or 2-(2-oxopyrrolidin-1-yl)ethyl.

In some preferred embodiments, compounds off the invention have the Formula Ia:



Ia

wherein X, R_4, R_5, m and n are as previously defiined.

In some preferred embodiments of Formula Iaa, m and n are 1, and R_4 and R_5 are independently hydrogen, methyl, butyl, benzyl, 2-ethylhexyl or 2-phenylethyl. IIn other preferred embodiments of Formula Ia, R_4 and R_5 arre independently benzyl or 2-phenylethyl.

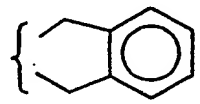
In further preferred embodiments of Formulaa Ia, m and n are 0, and R_4 and R_5 are independently methoxypheenyl or 2-phenylethyl.

In other preferred embodiments of Formula IIa, X is benzyloxy or *t*-butoxy. In some preferred embodiiments X, taken together with the carbonyl group of Formulla Ia to which X is attached, is monoisopropylidine-2-ketto-L-gulonyl or diisopropylidine-2-keto-L-gulonyl.

As used herein, the term "alkyl" is meant tto inclυde straight-chain, branched and cyclic hydrocarbon groups such as, for example, ethyl, isopropyl and cyclopropyyl groups. Alkyl groups can contain one or two sites of unssaturation;

i.e., carbon-carbon double or triple bonds. Preferred alkyl groups have 1 to about 10 carbon atoms. "Cycloalkyl" groups are cyclic alkyl groups. "Aryl" groups are aromatic cyclic compounds including but not limited to phenyl, tolyl, naphthyl, anthracyl, phenanthryl, pyrenyl, and xylyl. Preferred aryl groups include phenyl and naphthyl. The term "carbocyclic", as used herein, refers to cyclic groups in which the ring portion is composed solely of carbon atoms. The term "heterocyclic" refers to cyclic groups in which the ring portion includes at least one heteroatom such as O, N or S. "Heteroalkyl" groups are heterocycles containing solely single bonds within their ring portions, i.e. saturated heteroatomic ring systems. Heteroalkyl groups may contain sites of unsaturation outside their ring portions. Thus, for example, pyrrolidinonyl groups, which contain carbonyl carbon atoms within their ring systems, are heteroalkyl groups as defined herein. The term "lower alkyl" refers to alkyl groups of 1-4 carbon atoms. The term "halogen" refers to F, Cl, Br, and I atoms.

The term "aralkyl" denotes an alkyl group which is substituted with an aryl group, such as, for example, a benzyl group. Aralkyl groups can consist of two alkyl groups bound to a single aryl group, such as groups having the formula:



The term "aralkyloxy" denotes an aralkyl group attached through an oxygen atom. The term "heteroaryl" denotes aryl groups having one or more heteroatoms contained within an aryl ring. "Heteroaralkyl" groups are aralkyl groups which have one or more heteroatoms in their aryl ring portion.

The term "carbohydrate" includes monosaccharidess, disaccharides, and polysaccharides, as well as ttheir protected derivatives, such as, for example, monno- and diisopropylidine derivatives.

Because the β-keto phosphates, β-keto phospphinates, β-keto phosphonates, α-keto phosphonates, α-keto pphosphinates, and α-keto phosphine oxides of the invention inhhibit cysteine proteases and serine proteases, they caan be used in both research and therapeutic settings.

In a research environment, preferred compouunds having defined attributes can be used to screen for nattural and synthetic compounds which evidence similar charaacteristics in inhibiting protease activity. Inhibition of cysteine protease or serine protease activity can be meassured by determining the rate of inactivation of a proteaase using a compound of the invention. The compounds can allso be used in the refinement of *in vitro* and *in vivo* modelss for determining the effects of inhibition of particuular proteases on particular cell types or biologicall conditions. In a therapeutic setting, given the connection boetween cysteine proteases and certain defined disorderss, and serine proteases and certain defined disorders, compounds of the invention can be utilized to alleviate, mediate,. reduce and/or prevent disorders which are associated wiith abnormal and/or aberrant activity of cysteine proteases aand/or serine proteases.

In preferred embodiments, compositions are provided for inhibiting a serine protease or a cysteine proteaase comprising a compound of the invention. In otheer preferred embodiments, methods are provided for inhibiting serine proteases or cysteine proteases comprising contaacting a protease selected from the group consisting of sserine proteases and cysteine proteases with an inhibitcory amount of a compound of the invention.

The disclosed compounds of the invention arre useful for the irreversible inhibition of cysteine proteasees and serine proteases. As used herein, the terms "inhibit" and "inhibition" mean having an adverse effect on ennzymatic activity. The term "irreversible," when used too modify "inhibit". and "inhibition" means that such adverrse effect on catalytic activity can not be readily reversed. An inhibitory amount is an amount of a compound of the invention effective to inhibit a cysteine and/orr serine protease.

Pharmaceutically acceptable salts of the cyysteine and serine protease inhibitors also fall within the scope of the compounds as disclosed herein. The term "pharmaaceutically acceptable salts" as used herein means an inorgaanic acid addition salt such as hydrochloride, sulfate, annd phosphate, or an organic acid addition salt such as acetatee, maleate, fumarate, tartrate, and citrate. Examples of pharmaceutically acceptable metal salts are alkaali metal salts such as sodium salt and potassium salt, allkaline earth metal salts such as magnesium salt and calcium ssalt, aluminum salt, and zinc salt. Examples of pharmnaceutically acceptable ammonium salts are ammonium salt and tetramethylammonium salt. Examples of pharmaceuutically acceptable organic amine addition salts are saltts with morpholine and piperidine. Examples of pharmaceeutically acceptable amino acid addition salts are salts wwith lysine, glycine, and phenylalanine.

Compounds provided herein can be formulatedd into pharmaceutical compositions by admixture with pharmaceutically acceptable nontoxic excipients and carriers. As noted above, such compositions may be prepared for use in parenteral administration, particularrly in the form of liquid solutions or suspensions; or orall administration, particularly in the form of tabllets or capsules; or intranasally, particularly in the fform of

powders, nasal drops, or aerosols; or dermally, via, for example, transdermal patches; or prepared in otther suitable fashions for these and other forms of administraation as will be apparent to those skilled in the art.

The composition may conveniently be adminisstered in unit dosage form and may be prepared by any of tthe methods well known in the pharmaceutical art, for examplle, as described in *Remington's Pharmaceutical Sciencess* (Mack Pub. Co., Easton, PA, 1980). Formulations for parenteeral administration may contain as common excipients sterile water or saline, polyalkylene glycols such as poolyethylene glycol, oils and vegetable origin, hydrogenated naphthalenes and the like. In particular, biocompatible, biodegradable lactide polymer, lactide/glycolide copolymer, orr polyoxyethylene-polyoxypropylene copolymers may be useful excipients to control the release of the active compounds. Other potentially useful parenteral delivery systems for these active compounds include ethylene-vinyl accetate copolymer particles, osmotic pumps, implantable infusion systems, and liposomes. Formulations for inhalation administration contain as excipients, for examplle, lactose, or may be aqueous solutions containing, for exampple, polyoxyethylene-9-lauryl ether, glycocholate and deoxycholate, or oily solutions for administration in the form of nasal drops, or as a gel to be applied intranasally. Formulations for parenteral administration may also include glycocholate for buccal administration, a salicylate for rectal administration, or citric acid for vaginall administration. Formulations for transdermal patches are preferably lipophilic emulsions.

The materials of this invention can be employed as the sole active agent in a pharmaceutical or can be used in combination with other active ingredients, e.g., other growth factors which could facilitate neuronal survival or axonal regeneration in diseases or disorders.

The concentrations of the compounds described herein in a therapeutic composition will vary depending upon a number of factors, including the dosage of the drug to be administered, the chemical characteristics (e.g., hydrophobicity) of the compounds employed, and the route of administration. In general terms, the compounds of this invention may be provided in effective inhibitory amounts in an aqueous physiological buffer solution containing about 0.1 to 10% w/v compound for parenteral administration. Typical dose ranges are from about 1 µg/kg to about 1 g/kg of body weight per day; a preferred dose range is from about 0.01 mg/kg to 100 mg/kg of body weight per day. Such formulations typically provide inhibitory amounts of the compound of the invention. The preferred dosage of drug to be administered is likely, however, to depend on such variables as the type and extent of progression of the disease or disorder, the overall health status of the particular patient, the relative biological efficacy of the compound selected, and formulation of the compound excipient, and its route of administration.

As used herein, the term "contacting" means directly or indirectly causing at least two moieties to come into physical association with each other. Contacting thus includes physical acts such as placing the moieties together in a container, or administering moieties to a patient. Thus, for example administering a compound of the invention to a human patient evidencing a disease or disorder associated with abnormal and/or aberrant activity of such proteases falls within the scope of the definition of the term "contacting".

The invention is further illustrated by way of the following examples which are intended to elucidate the invention. These examples are not intended, nor are they to be construed, as limiting the scope of the disclosure.

Examples

Compounds of the invention were prepared by the following procedures.

Starting Materials:

Phenylalanine chloromethylketone can be purrchased from various commercial sources (e.g., BACHEM Bioscieence, Inc.) and was used as received. Benzyloxycarbonyl andd t-butoxycarbonyl protected dipeptide bromomethyl kketones were prepared from the corresponding diazomethylketonnes by treatment with HBr/AcOH or HBr (gas) according tto the standard procedures cited and described in Harbeeson, S. L. et al., *J. Med. Chem.* 1989, *32*, 1378-1392. (Morpholinylsulfonyl)-L-leucine was prepared acccording to Repine's procedure (Repine, J.T. et al., *J. Med.. Chem.*, 1992 *35*, 1032-1042). *N*-terminal protected dipeptide chloromethyl ketones were prepared from their corresponding *NN*-terminal protected-L-leucine and phenylalanine chloromethhylketone under isobutyl chloroformate mediated coupling cconditions (Rich D. L. et al., *J. Med. Chem.* 1992 *35*, 3802—3812). *N*-t-Butoxycarbonyl-L-leucinal was prepared from t-butoxycarbonyl-L-leucine (Goel, O. P. et al., *Orrg. Syn.* 1993, *Coll. Vol. VIII*, 68). Dialkyl (*2S*)-2-(t-butoxycarbonylamino)-1-hydroxy-4-methylpentyl phhosphonates were obtained by condensation of t-butoxycarbonyyl-L-leucinal with corresponding dialkyl phosphites according to literature procedures (Texier-Boullet, F. et al.., *Synthesis* 1982, 165). Two cyclic phosphinic acids were prrepared according to Montchamp's procedure (Montchamp, JJ. et al., *J Org. Chem.* 1995, *60*, 6076-6081). The disclosurees of Harbeson et al., Repine et al., Rich et al., Goeel et al., Texier-Boullet et al., and Montchamp et al. are hereby incorporated by reference in their entirety.

Analyses:

FAB mass spectra were obtained by M-Scan, Innc. Ion spray mass spectra were determined with Fisons VGG platform mass spectrometer.

Example 1: Intermediate

Benzyloxycarbonyl-L-leucyl-L-phenylalanyl bromomeethyl ketone (m.p. 135.5-136.5°C) was prepared by the procedurre described by Harbeson et al., *supra*.

Example 2: Intermediate

***t*-Butoxycarbonyl-L-leucyl-L-phenylalanyl bromometthyl ketone** (m.p. 120-122°C) was prepared by the procedure déescribed by Harbeson et al., *supra*.

Example 3: Intermediate

Diisopropylidine-2-keto-L-gulonyl-L-leucyl-L-phennylalanyl chloromethyl ketone (m.p. 74-75°C) was prepared bby a modification of the procedure described by Rich eet al., *supra*.

Example 4: Intermediate

Diisopropylidine-2-keto-L-gulonyl-L-leucyl-L-phennylalanyl iodomethyl ketone was prepared from diisopropyliddine-2-keto-L-gulonyl-L-leucyl-L-phenylalanyl chloromethyl kęętone with 1.5 eq. of NaI in acetone and used for the next sstep without purification.

Example 5: Intermediate

Morpholinylsulfonyl-L-leucyl-L-phenylalanyl cholooromethyl ketone (m.p.145-146.5°C) was prepared by a modifiication of the procedure described by Rich et al., *supra*.

Example 6: Intermediate

Morpholinylsulfonyl-L-leucyl-L-phenylalanyl iodomethyl ketone was prepared from morpholinylsulfonyl-L-leucyl-L-phenylalanyl chloromethyl ketone with 1.5 eq. of NaI in acetone and used for the next step without purification.

Example 7: Intermediate

Diphenethyl phosphate:

A solution of 0.79g (4.0 mmol) of *N,N*-diisopropyl methylphosphonamidic chloride in 0.6 mL of CH_2Cl_2 was stirred at 0°C under N_2 as a mixture of phenethyl alcohol (0.50g, 4.0 mmol) and pyridine (0.32g, 1.0eq.) in 0.6 mL of CH_2Cl_2 was added. The solution was warmed to room temperature and stirred overnight (~16h). The solution was then cooled to 0°C and 0.8 mL of MeOH and 2.4 mL of 30% H_2O_2 were slowly added. The mixture was warmed to room temperature and stirred for 5 hours, and the product was extracted with CH_2Cl_2 (2 X 10mL). The combined organic layers were washed with 10% Na_2SO_3 (10 mL), 1N HCl (10 mL), brine (10 mL), dried over magnesium sulfate and concentrated. Flash chromatography (50% ethyl acetate in hexane) gave 0.51 (39%) of the bis(phenethyl) methyl phosphate as a clear oil.

A solution of 0.26g (0.8 mmol) of bis(phenethyl) methyl phosphate in 3.2 mL of dry acetonitrile was stirred at 0°C under N_2 while 0.23 mL (2.18 eq.) of TMSBr was added dropwise. The solution was stirred at 0°C for 1..5 hours. The solvent was removed and the residue was dissolved in NaOH (1.0 eq.) in MeOH solution. After 30 minutes at room temperature, the solution was concentrated, and the white solid was taken up in ether (6.0 mL) and filtered to give sodium bis(phenethyl) phosphate.

A solution of sodium bis(phenethyl) phosphate (0.24 mg, 0.73mmol) in 1.0 mL of water was stirred as 2.0 mL of concentrated hydrochloric acid (2.0 mL) was added. The

organic layer was extracted with CH_2Cl_2 (3X6mL) arnd dried over magnesium sulfate. Concentration gave 0.18 g (81%) of bis(phenethyl) phosphate. MS: 305 m/z (M-1).

Example 8: Intermediate

Bis(2-cyclohexylethyl) phosphate was prepared acccording to the general procedure given for bis(phenethyl) phhosphate in Example 7. MS: 317 m/z (M-1).

Example 9: Intermediate

Bis(3-phenoxybenzyl) phosphate:

A solution of 0.79 ml (4.0 mmol) of *N,N*-diiisopropyl methylphosphonamidic chloride in 0.6 mL of CH_2Cl_2 was stirred at 0°C under N_2 as a mixture of 3-phenoxybenzyl aalcohol (1.6g, 8.0 mmol) and pyridine (0.32g, 1.0eq.) in 0.6 mL of CH_2Cl_2 was added. The solution was warmed to roomm temperature and stirred for 5 hours. The solutioon was then cooled to 0°C and 0.8 mL of MeOH and 2.4 mL of 300%H_2O_2 were slowly added. The mixture was warmed to room tempperature and stirred for 5 hours. The product was extracted wwith CH_2Cl_2 (2 X 10mL). The combined organic layers were wasshed with 10% Na_2SO_3 (10 mL), 1N HCl (10 mL), brine (10 mL),, dried over magnesium sulfate and concentrated. Flash chromaatography (50% ethyl acetate in hexane) gave 0.51g (39%) off the bis(3-phenoxybenzyl) methyl phosphate as a clear oil.

A solution of 0.48g (1.0 mmol) of bis(3-pheenoxybenzyl) methyl phosphate in 10 mL of toluene was stirred at rt under N_2 while 0.125g (1.1 eq.) of 1,4-diazabicyclo[2.2?.2]octane was added. The solution was refluxed for 4.0 hourrs. The solvent was removed and residue was diluted in 5%% HCl solution (10 mL), extracted with EtOAc (3X10mL) aand dried over magnesium sulfate. Concentration gave 0.33 gg (72%) of bis(3-phenoxybenzyl) phosphate. MS: 461 m/z (M-11).

Example 10: Intermediate

Bis(2-methylbenzyl) phosphate was prepared according to the general procedure given for of bis(3-phenoxybenzyyl)phosphate in Example 9. MS: 305 m/z (M-1).

Example 11: Intermediate

5-Benzyloxy-2-hydroxy-1,3,2-dioxaphosphorinane 2--oxide

A solution 0.5g (2.75 mmol) of 2-benzyloxy-11,3-propanediol in 3.0 mL of pyridine was stirred at 0 °C under N_2 as 0.37g (2.5 mmol) of methyl dichlorophosphatee was added dropwise over 15 mins to keep the solution under 10 °C. The cold bath was removed and the reaction mixture waas stirred overnight at 20 °C(~14h). The mixture was filterred, and washed with benzene (10 mL), and the filtrate waśś evaporated. The residue was dissolved in benzenee : CH_2Cl_2 (1:1, 20 mL), washed with H_2O (10 mL), saturated $NaHCO_3$ (10 mL), saturated NaCl (10 mL) and dried over magnessium sulfate. Evaporation afforded 0.26 g (40%) of 5--benzyloxy-2-methyl-1,3,2-dioxaphosphorinane-2-oxide.

A solution of 0.19 g (0.75 mmol) of (2-benzyloxy)propylene methyl phosphate in 7.5 mL off toluene was stirred at rt under N_2 while 0.093g (1.1 eq.)ı of 1,4-diazabicyclo[2.2.2]octane was added. The solutionn was refluxed for 4.0 hours. The solvent was removed and the residue was diluted in 5% HCl solution (10 mL), eextracted with EtOAc (3X10mL) and dried over magnesium sulffate. Concentration gave 0.14g (74%) of 5-benzyloxy-2-hhydroxy-1,3,2-dioxaphosphorinane-2-oxide. MS: 243 m/z (MM-1).

Example 12: Intermediate

Methyl hydrogen *N,N*-diisopropylphosphonamidate:

A solution of 0.395g (2.0 mmol) of methyl *NN,N*-diisopropylphosphonamidic chloride in 0.3 mL of CCH_2Cl_2 was stirred at 0°C under N_2 as a mixture of benzyl alccohol ,

(0.17g, 1.6 mmol) and triethylamine (0.2g, 1.0eq.) in 0.3 mL of CH_2Cl_2 was added. The solution was warmed to room temperature and stirred overnight. The solution was cooled to 0°C and 0.4 mL of MeOH and 1.2 mL of 30% H_2O_2 were slowly added. The mixture was warmed to room temperature and stirred for 0.5 hours. The product was extracted with CH_2Cl_2 (2X8mL). The combined organic layers were washed with 10% Na_2SO_3 (8 mL), 1N HCl (8 mL), brine (8 mL), and dried over magnesium sulfate. Concentration gave 0.45g (98%) of *N,N*-diisopropylmethyl benzyl phosphonamidate as a clear oil.

A suspension of 57 mg of 20% $Pd(OH)_2/C$ in a solution of *N,N*-diisopropylmethyl benzyl phosphonamidate (57 mg, 0.2 mmol) in 3.0 mL of ethyl acetate was stirred under H_2 (1 atm) at room temperature for 2 hours. The catalyst was filtered through celite and the filtrate was concentrated to give 27 mg (69%) of the clean product.

Example 13: Intermediate

Bis(2-phenylethyl)phosphinic acid:

(2-Bromoethyl)benzene (6.8 mL, 9.21 g, 49.8 mmol) was added to magnesium turnings (1.20 g, 49.4 mmol) suspended in ether (20 mL) under nitrogen. When the reaction initiated, it was cooled and stirred for 40 minutes at 0°C, 40 minutes at 20°C, and 2.5 hours at reflux. Ether (10 mL) was added to the resulting Grignard reagent at 0°C. Dimethyl phosphite (1.22 mL, 1.86 g, 16.9 mmol) was added dropwise, resulting in a vigorous reaction and formation of a gelatinous precipitate.

The mixture was stirred with a glass rod, and then magnetically for 22 hours at 20°C. The heterogeneous mixture was cooled to 0°C, and 1 M HCl (15 mL) was added slowly, followed by acidification with 6 M HCl. The ether phase was separated, and the aqueous phase was extracted three times with EtOAc. The combined organic phases were rinsed with saturated NaCl and dried over $MgSO_4$ and the

solvent evaporated to afford crude bis(2-phenylethyl)phosphinous acid (4.26 g) which was carried forward.

Hydrogen peroxide (0.45 mL, 30%, 4.36 mmol) was added dropwise over 1 minute to crude bis(2-phenylethyl)phosphinous acid (1.12 g, 4.34 mmol) in methanol (6.5 mL). After 16 hours, the solvent was evaporated. The residue was basified with 1 M NaOH and extracted twice with hexanes. The aqueous layer was acidified with 12 M HCl, and the precipitate was filtered, rinsed with water, and dried in vacuo, affording crude product (628 mg) mp 70 - 77°C, which was recrystallized from hot ethanol - water (50:50) to give bis(2-phenylethyl)phosphinic acid (364 mg) as a white solid, mp 84 - 87°C. NMR δ 2.02 (4H, m), 2.94 (4H, q), 6.8 (1H, br. s), 7.24 (10H, m).

Analysis calculated for $C_{16}H_{19}O_2P$: C, 70.06; H, 6.98. Found: C, 69.86; H, 6.92.

Example 14: Intermediate

Bis[(2-methyl)phenyl]phosphinic acid was prepared according to the general procedure given for bis(2-phenylethyl)phosphinic acid in Example 13. MS: 245 m/z (M-1).

Example 15: Intermediate

Dipentylphosphinic acid was prepared according to the general procedure given for bis(2-phenylethyl)phosphinic acid
in Example 13. MS: 189 m/z (M-1).

Example 16: Intermediate

Ethyl phenylphosphinate:

This compound was prepared according to the procedure described by Froestl, W. et al., *J. Med. Chem.*, 1995, *38*,

3313-3331. From phenyl dichlorophosphine (10.0 gg, 55.9 mmol), ethanol (9.1 ml, 156 mmol) and triethylamiine (10.1 ml, 72.6 mmol) in anhydrous diethyl ether (100 mll) was obtained 7.7 g (81%) of the title compound as a ccolorless mobile oil following distillation; bp 72-74°C (0..15 mm Hg); analysis calculated for $C_8H_{11}O_2P$: C, 56.47; H, 6.!53; P, 18.20; Found: C, 56.21; H, 6.47; P, 17.87.

Example 17: Intermediate
Ethyl (ethyl)(phenyl)phosphinate:

A slurry of sodium hydride (0.13 g of a 60% suspension in mineral oil, 3.2 mmol) in anhydrous THF (10 mll) was treated dropwise with a solution of ethyl phenylpphosphinate (0.50 g, 2.9 mmol) over one hour via a syring pummp. The mixture was allowed to stir an additional 30 minuutes before the addition of ethyl iodide (0.26 ml, 3.2 mmol).. After 45 minutes the reaction was quenched with 10% aqueouus ammonium chloride (5 ml) and poured into a separatory funnnel containing ethyl acetate (50 ml). The organic phhase was washed with water, saturated aqueous sodium bicarrbonate and brine before being dried over magnesium sulfate, filtered and concentrated to afford 0.30 g (52%) of the tiitle compound as a colorless mobile oil following flassh chromatography on silica gel (50% ethyl acetate/hhexane); MS: 199 m/z $(M+H)^+$.

Example 18: Intermediate
(Ethyl)(phenyl)phosphinic acid:

A solution of ethyl (ethyl)(phenyl)phosphinaate (130 mg, 0.66 mmol) in ethanol (0.5 ml) was treated with 4N HCl (1 ml) and refluxed for 22 hours. Tlc analysis revvealed some residual starting material. The ethanol was remaoved on the rotary evaporator, an additional aliquot of 4N HCl (1 ml) was added, and reflux was resumed for a further six hours

whereupon tlc analysis revealed complete consumption of starting material. The mixture was lyophillized to afford 110 mg (99%) of the title compound as a white solid; MS: 171 m/z $(M+H)^+$; analysis calculated for $C_8H_{11}O_2P$: C, 56.47; H, 6.53; P, 18.20; Found: C, 56.23; H, 6.35; P, 18.52.

Example 19: Intermediate

1-Chloro-3-(N-morpholino)propane was prepared according to the procedure described in Adams, R. R. et al., *J. Amer. Chem. Soc.*, **1945**, *67*, 735-738. From morpholine (15.0 g, 172 mmol), and 1-bromo-3-chloropropane (11.3 ml, 115 mmol) in refluxing benzene (50 ml) was obtained 11.4 g (400%) of the title compound as a colorless mobile oil; bp 55-558 °C, 0.4 mmHg; MS: 164, 166 m/z $(M+H)^+$, chlorine isotope pattern.

This compound was seen to be somewhat unstable at ambient temperature and was stored at -10°C and used as rapidly as possible or converted to the corresponding hydrochloride salt for long-term storage. The hydrochloride salt was prepared by treating an ethereal solution of the free base with 1N HCl in ether (1.1 equiv.), followed by filtration and washing with ether to give a fine white powder upon drying under vacuum; mp 176-178°C; analysis calculated for $C_7H_{15}Cl_2NO$: C, 42.01; H, 7.57; N, 7.00; Cl, 35.43; Found: C, 41.26; H, 7.37; N, 6.80; Cl, 355.47.

Example 20: Intermediate

Ethyl [3-(morpholin-4-yl)propyl](phenyl)phosphinate:

This compound was prepared using the general procedure described in Example 17 for the preparation of ethyl (ethyl)(phenyl)phosphinate, except that the reaction was conducted in anhydrous DMF instead of THF. From ethyl phenylphosphinate (0.5g, 2.9 mmol) and 1-chloro-3-(N-morpholino)propane (0.6 g, 3.5 mmol) was obtained 0.322 g (37%) of

the title compound as a colorless oil following flash chromatography on silica gel (10% methanol/ethyl acetate); MS: 298 m/z $(M+H)^+$, 320 m/z $(M+Na)^+$.

Example 21: Intermediate

[3-(Morpholin-4-yl)propyl](phenyl)phosphinic acid:

A solution of ethyl [3-(morpholin-4-yl)propyl](phenyl)phosphinate (300 mg, 1.0 mmol) in 4N HCl (5 ml) was refluxed for 18 hours. Lyophilization afforded 310 mg (100%) of the title compound as an amorphous hygroscopic solid; MS: 270 m/z $(M+H)^+$.

Example 22: Intermediate

2-Hydroxy-1*H*-phosphindoline 2-oxide was prepared by the procedure described by Montchamp et al., *supra*. MS: 167 m/z (M-1).

Example 23: Intermediate

1-Hydroxyphosphol-3-ene 1-oxide was prepared by the procedure described by Montchamp et al., *supra*. MS: 117 m/z (M-1).

Example 24: Intermediate

Dibenzyl phenylphosphonate:

A stirred solution of phenylphosphonic acid (1.0 g, 6.3 mmol), benzyl alcohol (1.6 ml, 15.8 mmol) and triphenylphosphine (4.2 g, 15.8 mmol) in anhydrous THF (60 ml) under N_2 was treated dropwise with diethyl azodicarboxylate (2.5 ml, 15.8 mmol) over five minutes. The mixture was stirred for two hours before being concentrated under vacuum. The residue was stirred with acetone-hexane (15 ml, 1/1) at 5°C for 1-2 hours and the resulting precipitate of triphenylphosphine oxide was collected by

suction filtration and discarded. The filtrate was concentrated in vacuo and the residue was stirred a second time with acetone-hexane (15 ml, 1/1) at 5°C for 1-2 hours to provide an additional crop of triphenylphosphiine oxide following filtration. The filtrate was concentrated as before to give 5.2 g of the crude product as a nearly colorless oil. Flash chromatography (silica gel,, 10-40% ethyl acetate/hexane) gave 1.6 g (76%) of the tittle compound as a colorless oil. NMR δ 7.85-7.30 (15H, m), 5..15-5.00 (4H, m); MS: 339 m/z (M+H), 361 m/z (M+Na).

Example 25: Intermediate

Monobenzyl phenylphosphonate:

A solution of dibenzyl phenylphosphonate (3440 mg, 1.0 mmol) and 1,4-diazabicyclo[2.2.2]octane (124 mg, 1.1 mmol) in toluene (5 ml) was refluxed for 12-18 hours. Ethyl acetate (25 ml) was added and the mixture was wasshed with 2N HCl (2 x 15 ml), water (15 ml) and finally brine (15 ml) before being dried ($MgSO_4$), filtered and concentrrated to provide 215 mg (87%) of the title compound as a ccolorless oil which was used without further purification. NMR δ 7.85-7.25 (10H, m), 5.05 (2H, d); MS: 248 m/z (M++H), 271 m/z (M+Na).

Example 26: Intermediate

Dibenzyl methylphosphonate was prepared by the geeneral procedure described for dibenzyl phenylphosphonatte, Example 24. From methylphosphonic acid (1.0 g, 10.4 mmol)), benzyl alcohol (2.7 ml, 26 mmol), triphenylphosphine (6,,8 g, 26 mmol) and diethyl azodicarboxylate (4.1 ml, 26 mmmol) in anhydrous THF (100 ml) was obtained 1.7 g (58%) oof the title compound as a colorless oil following flash chrommatography on silica gel (30% ethyl acetate/hexane).

MS: 277 m/z $(M+H)^+$, 299 m/z $(M+Na)^+$.

Example 27: Intermediate

Monobenzyl methylphosphonate was prepared by the general procedure described for the preparation of monobenzyl phenylphosphonate in Example 25. From dibenzyl methylphosphonate (500 mg, 1.8 mmol), and 1,4-diazabicyclo[2.2.2]octane (223 mg, 2.0 mmol) in refluxing toluene (10 ml) after 21 hours was obtained 80 mg (24%) of the title compound as a pale yellow oil which was used without further purification. MS: 185 m/z (M-H)..

Example 28: Intermediate

Benzyl 2-(morpholin-4-yl)ethyl phenylphosphonate:

A mixture of monobenzyl phenylphosphonate (1115 mg, 0.46 mmol), N-(2-chloroethyl)morpholine hydrochloride (95 mg, 0.51 mmol) and potassium carbonate (140 mg, 1.0 mmmol) in anhydrous DMF was stirred at 65°C for 22 hours. Following dilution with ethyl acetate (40 ml), the mixture was washed with water four times and finally brine before being dried over magnesium sulfate, filtered and concentrated to leave 124 mg (74%) of the title compound as a pale yelllow oil which was used without further purification. MS: 362 m/z $(M+H)^+$.

Example 29: Intermediate

2-(Morpholin-4-yl)ethyl phenylphosphonate:

A mixture of benzyl 2-(morpholin-4-yl)ethyl phenylphosphonate (110 mg, 0.30 mmol) and 10% Pd/C (100 mg) in ethanol (5 ml) was hydrogenated under 40psi H_2 on a Paar apparatus for two hours at ambient temperature. Filtration and concentration afforded 76 mg of the title compound as a colorless viscous oil which was used without furtther purification. MS: 272 m/z $(M+H)^+$.

Example 30: Intermediate

Benzyl phenylphosphonic chloride:

A solution of dibenzyl phenylphosphonate (1..5 g, 4.4 mmol) and diazabicyclo[2.2.2]octane (0.55 g, 4.9 mmol) in toluene (35 ml) was refluxed for 5 hours. The miixture was cooled in an ice-water bath and treated with one drop of anhydrous DMF followed by oxalyl chloride (0.81 mml, 9.3 mmol). After being stirred for 30 minutes the miixture was filtered and concentrated to give 0.75 g (63%) off the title compound as a pale yellow oil which was used withhout further purification. MS: 267 m/z $(M+H)^+$, 289 m/z $(M+Na)^+$..

Example 31: Intermediate

Benzyl 2-(2-oxopyrrolidin-1-yl)ethyl phenylphosphhonate:

An ice-cooled solution of 1-(2-hydroxyethyl))-2-pyrrolidinone (160 mg, 1.2 mmol) and triethylamine (0.17 ml, 1.2 mmol) in dichloromethane (5 ml) was treated ddropwise over 5 minutes with a solution of benzyl phenylphhosphonic chloride (330 mg, 1,2 mmol) in dichloromethane (55 ml). The mixture was allowed to slowly warm to ambient temmperature while stirring overnight. The mixture was pouredd into a separatory funnel containing ethyl acetate (50 mll) and water (25 ml). The organic phase was washed once more with water and finally brine before being dried over magnesiium sulfate, filtered and concentrated to afford 200 mg (45%) of the title compound as a yellow mobile oil. MS: 360 m//z $(M+H)^+$, 382 m/z $(M+Na)^+$.

Example 32: Intermediate

2-(2-Oxopyrrolidin-1-yl)ethyl phenylphosphonic acid was prepared according to the general procedure descrribed for the preparation of 2-(morpholin-4-yl)ethyl phenyllphosphonate in Example 29 From benzyl 2-(2-oxopyrrolidin-1-yll)ethyl phenylphosphonate (170 mg, 0.47 mmol) and 10% Pd//C (100 mg)

in ethanol (15 ml) was obtained 107 mg (84%) of tthe title compound. MS: 270 m/z $(M+H)^+$, 292 m/z $(M+Na)^+$.

Example 33: Methods for Preparing Inhibitors

Methods A, B, C, D and E are representative methods for preparing compounds of the invention.

Method A: To a solution of the appropriate bromo or iodoketone (0.1-0.2 mmol) in 1.0-2.0 mL of DMF waas added anhydrous potassium fluoride (3.5 eq.) under N_2. After the mixture was stirred at room temperature for 5 minutes, a phosphate, phosphonate, phosphinic acid, or phosphonamidate (1.2 eq.) was added, and the mixture was stirred for 3-72 hours. The reaction mixture was diluted with CH_2Cl_2 and filtered through celite. The solution was washed with water, 5% $NaHCO_3$ solution, 5% aqueous citric acid, brine and dried over magnesium sulfate. Purification by flash chromatography or crystallization afforded the desired product.

Method B: A solution of the appropriate bromo or iodoketone (0.1-0.2 mmol) in 0.5-1.0 mL of CH_2Cl_2 was stirred at 0°C under Ar while diisopropylethylamine (3.3 eq.) waas added dropwise by syringe. After 5 minutes, a phosphatte or phosphinic acid (1.2 eq.) was added, and the reaction was warmed to room temperature and stirred for 3-24 hhours. The reaction was diluted with ethyl acetate and washed with 5% $NaHCO_3$ solution, 5% aqueous citric acid, brine andd dried over $MgSO_4$. Purification by flash chromatography or crystallization afforded the desired product.

Methods C, D and E are representative methodds for preparing compounds of the invention from dialkyll (*2S*)-2-(t-butoxycarbonylamino)-1-hydroxy-4-methylpentyl phoosphonates.

Method C: Dialkyl (*2S*)-2-(t-butoxycarbonylamino)--1-hydroxy-4-methylpentyl phosphonates were prepared from Booc-L-Leucinal with dialkyl phosphites by a modificatioon of the procedure described by Texier-Boullet et al., *suppra*.

Method D: The Boc protecting group was removed bby treating the dialkyl (*2S*)-2-(t-butoxycarbonylamino)-1-hydrroxy-4-methylpentyl phosphonate with 4N HCl in dioxane. The solvent was evaporated in vacuo, and the residue was triturated with diethyl ether. The crude white ssolid, 2-amino-1-hydroxy-4-methylpentyl phosphonate HCl saalt, was used directly for the next step.

To a solution of Cbz-Leu-OH (1.0 mmol) in DMMF (5 mL) was added 2-amino-1-hydroxy-4-methylpentyl phosphhonate HCl salt (1.0 mmol), iPr$_2$NEt (1.0 mmol), HOBt (1.0 mmaol) and DCC or BOP (1.0 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 5 min. and for 2-24 h at room temperrature. Dicyclohexylurea was filtered off (when DCC was uused) and the solvent was evaporated. The residue was disssolved in ethyl acetate (20 mL) and washed with 3% of citriic acid, 5% of $NaHCO_3$, and brine. The organic layer was drieed over MgSO4. The crude material was purified by flash chromatography (ethyl acetate in hexane).

Method E: A solution of Cbz-L-leucyl-L-2-amino-((*R,S*)-1-hydroxy-4-methylpentylphosphonate (0.2 mmol) and t-BuOH (0.41 mmol) in CH_2Cl_2 (5 mL) was stirred as Dess-MMartin periodinane (0.4 mmol) was added. The reaction was stirred at room temperature for 2-3 h. The reaction mixtture was diluted with CH_2Cl_2 and filtered through celite. The filtrate was washed with 10% $Na_2S_2O_3$ and dried overr $MgSO_4$ or

directly concentrated to dryness. The crude prodduct was purified by preparative HPLC or crystallization. The following Examples list method, starting materialls, reaction times, purification methods, yields, physical propperties, elemental analyses and/or mass spectra.

Example 34:

Dibenzyl (3*S*)-[3-[(N-Benzyloxycarbonyl-L-leucyl)aamino]-2-oxo-4-phenylbutyl] phosphate:

Method A; Cbz-L-leucyl-L-phenylalanyl bromomethyll ketone; dibenzyl phosphate (Aldrich Chemical Co.); 24h; fflash chromatography (30% ethyl acetate in hexane); yield 44%; mp 117-118°C; FABMS: 687 m/z (M+H).

Analysis calculated for $C_{38}H_{43}N_2O_8P$: C, 66.46; H, 6.31; N, 4.08. Found: C, 66.18; H, 5.94; N, 4.41.

Example 35:

Dibenzyl (3*S*)-[3-[(N-t-Butoxycarbonyl-L-leucyl)amnino]-2-oxo-4-phenylbutyl] phosphate:

Method A; Boc-L-leucyl-L-phenylalanyl bromomethyll ketone; dibenzyl phosphate; 17 hours; flash chromatographyy (2:1 ethyl acetate : hexane); yield 46%; mp 84-85°C; MMS: 653 m/z (M+H); 675 m/z (M+Na).

Analysis calculated for $C_{35}H_{45}N_2O_8P$: C, 64.40; H, 6.95; N, 4.29. Found: C, 64.32; H, 7.10; N, 4.75.

Example 36:

Dibenzyl (3*S*)-[3-[(N-morpholinylsulfonyl-L-leucyll)amino]-2-oxo-4-phenylbutyl] phosphate:

Method A; morpholinylsulfonyl-L-leucyl-L-phenylallanyl iodomethyl ketone; dibenzyl phosphate; 24 hours; flash chromatography (50% ethyl acetate in hexane); yieeld 38%; mp 52-52.5°C; MS: 702 m/z (M+H); 724 m/z (M+Na).

Analysis calculated for $C_{34}H_{44}N_3O_9PS$: C, 58.199; H, 6.32; N, 5.99. Found: C, 57.25; H, 6.25; N, 6.31.

Example 37:

Dibenzyl (3*S*)-[3-[(N-diisopropylidine-2-keto-L-guulonyl-L-leucyl)amino]-2-oxo-4-phenylbutyl] phosphate:

Method A; Diisopropylidine-2-keto-L-gulonyl-L-leuucyl-L-phenylalanyl iodomethyl ketone; dibenzyl phosphatte; 20 hours; flash chromatography (50% ethyl acetate inn hexane); yield 41%; mp 61-62°C; MS: 809 m/z (M+H); 831 m/zz (M+Na).

Analysis calculated for $C_{42}H_{53}N_2O_{12}P.0.7\ H_2O$: CC, 61.40; H, 6.67; N, 3.41. Found: C, 61.26; H, 6.56; N, 3.300.

Example 38:

Dibenzyl (3*S*)-[3-[(N-monoisopropylidine-2-keto-L--gulonyl-L-leucyl)amino]-2-oxo-4-phenylbutyl] phosphate):

A solution of 12.1 mg (0.015mmol) of dibenzyyl (3*S*)-[3-[(N-diisopropylidine-2-keto-L-gulonyl-L-leucyl)ammino]-2-oxo-4-phenylbutyl] phosphate in 0.5 mL of THF was stiirred at room temperature as 0.5 mL of 1.0 N HCl was addedd. The mixture was stirred at room temperature for 4 houurs. The solution was diluted with 15 mL of CH_2Cl_2, washed with water (2x5mL), brine (5 mL), dried over magnesium sulfaate. Concentration of the solution gave 8.1 mg (70%) of the product. MS: 769 m/z (M+H); 791 m/z (M+Na).

Example 39:

Bis(2-methylbenzyl) (3*S*)-[3-[(N-Benzyloxycarbonyll-L-leucyl)amino]-2-oxo-4-phenylbutyl] phosphate:

Method A; Cbz-L-leucyl-L-phenylalanyl bromomethyll ketone; bis(2-methylbenzyl) phosphate; 24h; flash chromattography (50% ethyl acetate in hexane); yield 15%; mp 87.55-88.5 °C; MS: 737 m/z (M+Na).

Example 40:

Bis(3-phenoxybenzyl) (3*S*)-[3-[(N-Benzyloxycarbonyyl-L-leucyl)amino]-2-oxo-4-phenylbutyl] phosphate:

Method A; Cbz-L-leucyl-L-phenylalanyl bromomethyll ketone; bis(3-phenoxybenzyl) phosphate; 20h; flash chromaatography (50% ethyl acetate in hexane); yield 20%; mp 71.55-73 °C; MS: 871 m/z (M+H); 893 m/z (m+Na).

Example 41:

Dihydrogen (3*S*)-[3-[(N-t-Butoxycarbonyl-L-leucyl))amino]-2-oxo-4-phenylbutyl] phosphate:

A suspension of 30 mg of 20% $Pd(OH)_2$ in a soolution of dibenzyl (3*S*)-[3-[(N-t-Butoxycarbonyl-L-leucyl)ammino]-2-oxo-4-phenylbutyl] phosphate (30 mg, 0.046 mmol) in 11.0 mL of ethyl acetate was stirred under H_2 (1 atm) at roomm temperature for 4 hours. The catalyst was filterred through Celite™ and the filtrate was concentrated to givee the crude product. Flash chromatography (10% MeOH in CH_2Cl_{22}) gave 8 mg of pure product. MS: 471 m/z (M-1).

Example 42:

Dimethyl (3*S*)-[3-[(N-Benzyloxycarbonyl-L-leucyl)aamino]-2-oxo-4-phenylbutyl] phosphate:

Method B; Cbz-L-leucyl-L-phenylalanyl bromomethyll ketone; dimethyl phosphate (Pfaltz & Bauer Inc.); 24 hourrs; flash chromatography (50% ethyl acetate in hexane); yieeld 29%; mp 87-88.5°C; MS: 535 m/z (M+H); 557 m/z (M+Na).

Example 43:

Dibutyl (3*S*)-[3-[(N-Benzyloxycarbonyl-L-leucyl)ammino]-2-oxo-4-phenylbutyl] phosphate:

Method A; Cbz-L-leucyl-L-phenylalanyl bromomethyll ketone; dibutyl phosphate (Fluka Chemical Co.); KF/AlO3 ((substituted for KF, 40% Aldrich Chemical Co.); 30h; flash chrromatography

(30% ethyl acetate in hexane) and recrystallization from ether/petroleum ether; yield 35%; mp 76-77°C; MS: 619 m/z (M+H); 641 m/z (M+Na).

Analysis calculated for $C_{32}H_{47}N_2O_8P$: C, 62.12;; H, 7.66; N, 4.53. Found: C, 62.21; H, 7.64; N, 4.48.

Example 44:

Bis(2-ethylhexyl) (3*S*)-[3-[(N-Benzyloxycarbonyl-IL-leucyl)amino]-2-oxo-4-phenylbutyl] phosphate:

Method A; Cbz-L-leucyl-L-phenylalanyl bromomethyll ketone; bis(2-ethylhexyl) phosphate (Aldrich Chemical Co.); 24h; flash chromatography (30% ethyl acetate in hexanee); yield 25%; mp 88-89.5°C; FABMS: 731 m/z (M+H).

Analysis calculated for $C_{40}H_{63}N_2O_8P$: C, 65.73;; H, 8.69; N, 3.83. Found: C, 65.64; H, 8.42; N, 3.96.

Example 45:

Bis(2-cyclohexylethyl) (3*S*)-[3-[(N-t-Butoxycarbonnyl-L-leucyl)amino]-2-oxo-4-phenylbutyl] phosphate:

Method A; Cbz-L-leucyl-L-phenylalanyl bromomethyll ketone; bis(2-cyclohexylethyl) phosphate; 24h; flash chrcomatography (50% ethyl acetate in hexane); yield 13%; mp 51-52.5 °C; FABMS: 715 m/z (M+Na).

Example 46:

Diphenethyl (3*S*)-[3-[(N-Benzyloxycarbonyl-L-leucyyl)amino]-2-oxo-4-phenylbutyl] phosphate:

Method A; Cbz-L-leucyl-L-phenylalanyl bromomethyll ketone; bis(phenethyl) phosphate; 24 hours; flash chromattography (50% ethyl acetate in hexane); yield 62%; m.p. 89-90°C; MS: 715 m/z (M+H); 737 m/z (M+Na).

Analysis calculated for $C_{40}H_{47}N_2O_8P$: C, 67.20;; H, 6.63; N, 3.92. Found: C, 67.04; H, 6.64; N, 3.85.

Example 47:

1-[(3*S*)-3-[(N-Benzyloxycarbonyl-L-leucyl)amino]-22-oxo-4-phenylbutyl]oxy]-5-benzyloxy-1,3,2-dioxaphosphoriinane 2-oxide

Method A; Cbz-L-leucyl-L-phenylalanyl bromomethyll ketone; 5-benzyloxy-2-hydroxy-1,3,2-dioxaphosphorinane 2-oxxide; 16 hours; crystallization from ethyl acetate in hexaane; yield 10%; m.p. 150-151°C; MS: 675 m/z (M+Na).

Example 48:

Benzyl (3*S*)-[3-[(N-benzyloxycarbonyl-L-leucyl)amiino]-2-oxo-4-phenylbutyl] methylphosphonate:

Method A; Cbz-L-leucyl-L-phenylalanylbromomeethyl ketone; monobenzyl methylphosphonate; recrystalliization (ethyl acetate/hexane; yield 22%), mp 165-167°C. Analysis calculated for $C_{32}H_{39}N_2O_7P$: C, 64.62; H, 6.62. Founnd: C, 64.54; H, 6.30.

Example 49:

Benzyl (3S)-[3-[(N-Benzyloxycarbonyl-L-leucyl)amiino]-2-oxo-4-phenylbutyl]phenylphosphonate:

Method A; Cbz-L-leucyl-L-phenylalanyl bromommethyl ketone; monobenzyl phenylphosphonate; recrystalliization (ethyl acetate/hexane; yield 46%), mp 111-114°C, NMR δ, 7.90-7.00 (20H, m), 6.59 (1H, m), 5.25-4.50 (8H, m), 44.15-4.05 (1H, m), 3.18-3.05 (1H, m), 2.97-2.83 (1H, m), 1..62-1.25 (3H, m), 0.95-0.80 (6H, m), MS: 657 m/z (M+H), 6779 m/z (M+Na).

Example 50:

2-(Morpholin-4-yl)ethyl (3*S*)-[3-[(N-benzyloxycarbonyl-L-leucyl)amino]-2-oxo-4-phenylbutyl] phenylphosphonate hydrochloride:

Method A; Cbz-L-leucyl-L-phenylalanylbromomethyl ketone; 2-(morpholin-4-yl)ethyl phenylphosphonate; 7 hours;; reverse-phase HPLC; yield 12% of a white amorphous solid which was extremely hygroscopic. A sample (9mg) was dissolved in acetonitrile (2 ml) and 2N HCl and subjected to lyophillization to give 8 mg of the title compound as a white amorphous powder. MS: 680 m/z $(M+H)^+$.

Example 51:

(3*S*)-[3-[(N-Benzyloxycarbonyl-L-leucyl)amino]-2-oxo-4-phenylbutyl] 2-(2-oxopyrrolidin-1-yl)ethyl phenylphosphonate:

Method A; Cbz-L-leucyl-L-phenylalanylbromomethyl ketone; 2-(2-oxopyrrolidin-1-yl)ethyl phenylphosphonic acid; 24 hours; precipitation from diethyl ether; yield 17%; MS: 678 m/z $(M+H)^+$, 700 m/z $(M+Na)^+$.

Example 52:

(3*S*)-[3-[(N-Benzyloxycarbonyl-L-leucyl)amino]-2-oxo-4-phenylbutyl] dimethylphosphinate:

Method A; Cbz-L-leucyl-L-phenylalanyl bromomethyll ketone; dimethylphosphinic acid; 24 hours; crystallizaticon (diethyl ether and petroleum ether); yield; 66% mp 121 - 1122 °C; MS: 503 m/z(M+H).

Analysis calculated for $C_{26}H_{35}N_2O_6P$: C, 62.14;; H, 7.02; N, 5.57. Found: C, 62.14; H, 6.85; N, 5.63.

Example 53:

(3*S*)-[3-[(N-Benzyloxycarbonyl-L-leucyl)amino]-2-oxo-4-phenylbutyl] dipentylphosphinate:

Method A; Cbz-L-leucyl-L-phenylalanyl bromomethyl ketone; dipentylphosphinic acid; 48 hours; flash chromatography (2:1 ethyl acetate in hexane); yield; 10% mp 112.5-114 °C; MS: 615 m/z(M+H).

Example 54:

(3*S*)-[3-[(N-Benzyloxycarbonyl-L-leucyl)amino]-2-oxo-4-phenylbutyl] bis(2-phenylethyl)phosphinate:

Method A; Cbz-L-leucyl-L-phenylalanyl bromomethyl ketone; bis(2-phenylethyl)phosphinic acid; 4.5 hours; flash chromatography (EtOAc-hexanes 75:25); yield 72 %; mp 95 - 100 °C (softens 80 °C). MS: 683 (M+H), 705 (M+Na). NMR δ 0.91 (6H, m), 1.50 (3H, m), 2.09 (4H, m), 2.89 (4H, m), 3.14 (1H, m), 4.16 (1H, m), 4.54 (1H, m), 5.08 (2H, ab-q), 5.10 (1H, d), 6.84 (1H, d), 7.24 (20H, m).

Analysis calculated for $C_{40}H_{47}N_2O_6P$: C, 70.36;; H, 6.94; N, 4.10. Found: C, 69.97; H, 7.02; N, 3.98.

Example 55:

(3*S*)-[3-[(N-Benzyloxycarbonyl-L-leucyl)amino]-2-oxo-4-phenylbutyl] bis(2-methylphenyl)phosphinate:

Method A; Cbz-L-leucyl-L-phenylalanyl bromomethyl ketone; bis(2-methylphenyl)phosphinic acid; 15 hours; flash chromatography (50% ethyl acetate in hexane); yield; 6% mp 58-60.5 °C; MS: 655 (M+H).

Example 56:

(3*S*)-[3-[(N-t-Butoxycarbonyl-L-leucyl)amino]-2-oxo-4-phenylbutyl] bis(2-methylphenyl)phosphinate:

Method A; Boc-L-leucyl-L-phenylalanyl bromomethyl ketone; bis(2-methylphenyl)phosphinic acid; 24 hours; flash

chromatography (50% ethyl acetate in hexane); yield; 6.5% mp 69-71 °C; MS: 621 (M+H).

Example 57:

(3*S*)-[3-[(N-Benzyloxycarbonyl-L-leucyl)amino]-2-oxo-4-phenylbutyl] bis(4-methoxyphenyl)phosphinate:

Method A; Cbz-L-leucyl-L-phenylalanyl bromomethyll ketone; bis(4-methoxyphenyl)phosphinic acid; 3 hours; flaash chromatography (2.5:1 ethyl acetate in hexane); yield 60%; m.p.58-59°C; MS: 686 m/z (M+H); 709 m/z (M+Na).

Analysis calculated for $C_{38}H_{43}N_2O_8P.0.5\ H_2O$: C,, 65.60; H, 6.37; N, 4.03. Found: C, 65.71; H, 6.31; N, 4.083.

Example 58: (3*S*)-[3-[(N-Benzyloxycarbonyl-L-leucyl)amino]-2-oxo-4-phenylbutyl] (2-methoxyphenyl)(phenyl)phosphinate:

Method B; Cbz-L-leucyl-L-phenylalanyl bromomethyll ketone; (2-methoxyphenyl)-phenylphosphinic acid; 24h; crystallization from ether/petroleum ether; yield 38%; m.p.120-121°C; MS: 657 m/z (M+H); 679 m/z (M+Na)..

Analysis calculated for $C_{37}H_{41}N_2O_7P$: C, 67.67; H, 6.29; N, 4.27. Found: C, 67.11; H, 6.15; N, 4.13.

Example 59:

(3*S*)-[3-[(N-Benzyloxycarbonyl-L-leucyl)amino]-2-oxo-4-phenylbutyl] (3-methoxylphenyl)(phenyl)phosphinatce:

Method A; Cbz-L-leucyl-L-phenylalanyl bromomethyll ketone; (3-methoxylphenyl)(phenyl)phosphinic acid; 17 hours; crystallization (diethyl ether in pentane); yield; 97% mp 65-67 °C; MS: 657 (M+H).

Example 60:

(3*S*)-[3-[(N-Benzyloxycarbonyl-L-leucyl)amino]-2-oxo-4-phenylbutyl] (ethyl)(phenyl)phosphinate:

Method A; Cbz-L-leucyl-L-phenylalanylbromomethyl ketone; (ethyl)(phenyl)phosphinic acid; 15 hours; recrystallization (ethyl acetate/hexane); yield 50%; mp 141-144°C; analysis calculated for $C_{32}H_{39}N_2O_6P$: C, 66.41; H, 6.81; N, 4..84; P, 5.35; Found: C, 66.32; H, 6.72; N, 4.74; P, 5.21..

Example 61:

(3*S*)-[3-[(N-Benzyloxycarbonyl-L-leucyl)amino]-2-oxo-4-phenylbutyl] [3-(morpholin-4-yl)propyl](phenyl)phosphinate:

Method B (but conducted in DMF); Cbz-L-leucyl-L-phenylalanylbromomethyl ketone; [3-(morpholin-4-yl)propyl](phenyl)phosphinic acid; 18 hours; flash chromatography (silica gel, 10% methanol/ethyl accetate); yield 43%; MS: 270 m/z $(M+H)^+$.

Example 62:

(3*S*)-2-[3-[(N-Benzyloxycarbonyl-L-leucyl)amino]-2-oxo-4-phenylbutyl] 1*H*-phosphindoline 2-oxide:

Method A; Cbz-L-leucyl-L-phenylalanyl bromomethyll ketone; 2-hydroxy-1*H*-phosphinodoline 2-oxide; 15 hours; crystallization (ethyl acetate in hexane); yield;; 21%; MS: 699 m/z(M+Na).

Example 63:

(3*S*)-1-[[3-[(N-Benzyloxycarbonyl-L-leucyl)amino]-2-oxo-4-phenylbutyl]oxy]phosphol-3-ene 1-oxide:

Method A; Cbz-L-leucyl-L-phenylalanyl bromomethyll ketone; 1-hydroxyphosphol-3-ene 1-oxide; 17 hours; tritrated from diethyl ether; yield; 47% mp 136-137.5 °C; MS: 5227 m/z (M+H).

Example 64:

Ethyl (3*S*)-[3-[(N-benzyloxycarbonyl-L-leucyl)amiino]-2-oxo-4-phenylbutyl](phenyl)phosphinate:

Method A; Cbz-L-leucyl-L-phenylalanylbromomethyll ketone; ethyl phenylphosphinate; 22 hours; flash chromatcography (silica gel, 33% ethyl acetate/hexane); yield 37?%; MS: 579 m/z $(M+H)^+$; 601 m/z $(M+Na)^+$.

Example 65:

Methyl Hydrogen *N*-Benzyloxycarbonyl-L-leucyl-L-leucylphosphonate was prepared from method C-E.

Method C; Boc-Leu-H; dimethyl phosphite; 24h; yiield; 92%; MS: 348 m/z (M+Na).

Method D; Cbz-Leu-OH, dimethyl 2-amino-1-hyydroxy-4-methylpentyl phosphonate HCl salt; 24h; flash chromatograghy (5% MeOH in CH_2Cl_2); yield 14%; product; Dimethyll Cbz-L-leucyl-L-2-amino-(*R,S*)-1-hydroxy-4-methylpentyl]phosphonate; MS: 473 m/z (M+H).

A solution of dimethyl Cbz-L-leucyl-L-2-amiino-(*R,S*)-1-hydroxy-4-methylpentyl phosphonate (0.3 mmol, 1412 mg) in CH_3CN (1.2 mL) was stirred at room temperature unnder Ar as lithium bromide (0.95 mmol, 25 mg) was added. TThe reaction mixture was stirred overnight. The solvent was]removed and the crude product was used directly for the next: step.

Method E; methyl hydrogen Cbz-L-leucyl-L-2-amino-(*R,S*)-1-hydroxy-4-methylpentyl phosphonate; Dess-Martiin periodinane; 16 h; yield 65%; mp 57 °C (dec.); Mis 455 m/z (M-H).

Analysis calculated for $C_{21}H_{33}N_2O_7P$: C, 55.24;; H, 7.29; N, 6.14. Found: C, 55.44; H, 7.02; N, 6.03.

Example 66:

Dibutyl *N*-Benzyloxycarbonyl-L-leucyl-L-leucylphossphonate:

Method C; Boc-Leu-H; dibutyl phosphite; 24h;; yield; 47%; MS: 410 m/z (M+1).

Method D; Cbz-Leu-OH, dibutyl 2-amino-1-hydrroxy-4-*methylpentyl* phosphonates HCl salt; 36h; flash chromatograghy (40% hexane in EtOAc); yield 71%; product; dibutyl Cbz-L-leucyl-L-2-amino-(*R,S*)-1-hydroxy-4--methylpentyl phosphonate; MS: 557 m/z (M+H); 579 m/z (M+Na).

Method E; Dibutyl Cbz-L-leucyl-L-2-amino-(*R,,S*)-1-hydroxy-4-methylpentyl phosphonate; Dess-Martin periodinane; 5 h; yield 13% (after prep. HPLC); Ms 555 m/z (M+H); 577 m/z (M+Na).

Example 67:

[Benzyloxycarbonyl-L-leucyl-L-leucyl]bis(4-chlorophenyl)phosphine oxide:

Method C; t-Boc-Leu-H; bis(4-chlorophenyl)phosphiine oxide; 2.5 hours; yield 83% (2*S*)-[2-[(t-Butoxycarbonyl)aamino]-1-hydroxy-4-methylpentyl]bis(4-chlorophenyl)phosphiine oxide; MS: 486, 488 m/z $(M+H)^+$, dichloro isotope patterrn.

(2*S*)-[2-[(t-butoxycarbonyl)amino]-1-hydroxy--4-methylpentyl]bis(4-chlorophenyl)phosphine oxide wwas treated with 25% trifluoroacetic acid in dichloromethane for 1 hour. Yield 97%; (2*S*)-(2-Amino-1-hydroxy-4-methylpentyll)bis(4-chlorophenyl)phosphine oxide; MS: 386, 388 m/z $(MM+H)^+$, dichloro isotope pattern.

Method D; Cbz-Leu-OH; (2*S*)-[2-amino-1-hydroxxy-4-methylpentyl]bis(4-chlorophenyl)phosphine oxide; 14 hours; flash chromatography (silica gel, 50% ethyl acetaate/hexane); yield 48% [Benzyloxycarbonyl-L-leucyl-L-2-amino-((*R,S*)-1-hydroxy-4-methylpentyl]bis(4-chlorophenyl)phosphiine oxide; MS: 633, 635 m/z $(M+H)^+$; 655, 657 m/z $(M+Na)^+$, dicchloro isotope pattern.

Method E; [Benzyloxycarbonyl-L-leucyl-L-2-amino-(*R,S*)-1-hydroxy-4-methylpentyl]bis(4-chlorophenyl)phosphine oxide; Dess-Martin periodinane; one hour; yield 30%; MS: 631, 633 m/z $(M+H)^+$; 654, 656 m/z $(M+Na)^+$, dichloro isotope pattern.

Example 68:

Ethyl N-benzyloxycarbonyl-L-leucyl-L-leucyl(phenyl)phosphinate:

Method C; Cbz-Leu-H; ethyl phenylphosphinate; 23 hours; yield 75%; Ethyl (2*S*)-[2-[(benzyloxycarbonyl)amino]-1-hydroxy-4-methylpentyl](phenyl)phosphinate; MS: 420 m/z $(M+H)^+$; 442 m/z $(M+Na)^+$.

Hydrogenation over 10% Pd/C in ethanol, afforded 81% ethyl (2*S*)-(2-amino-1-hydroxy-4-methylpentyl)(phenyl)phosphinate; MS: 286 m/z $(M+H)^+$.

Method D; Cbz-Leu-OH; ethyl (2*S*)-(2-amino-1-hydroxy-4-methylpentyl)(phenyl)phosphonate; 4 hours; flash chromatography (silica gel, ethyl acetate); yield 67% ethyl [benzyloxycarbonyl-L-leucyl-(2*S*)-2-amino-(*R,S*)-1-hydroxy-4-methylpentyl](phenyl)phosphinate; MS: 533 m/z $(M+H)^+$; 555 m/z $(M+Na)^+$.

Method E; Ethyl benzyloxycarbonyl-L-leucyl-(2*S*)-2-amino-(*R,S*)-1-hydroxy-4-methylpentyl(phenyl)phosphinate; Dess-Martin periodinane; 4 hours; yield 92%; MS: 531 m/z $(M+H)^+$; 553 m/z $(M+Na)^+$.

Example 69:

Inhibition and Rate of Inactivation of Cysteine Protease Activity

To evaluate inhibitory activity, stock solutions (40 times concentrated) of each compound to be tested were prepared in 100% anhydrous DMSO and 5 µl of each inhibitor preparation were aliquoted into each of three wells of a 96 well plate. Calpain I, prepared by a modification of the

method of W. J. Lee et al. (Biochem. Internatl. 222: 163-171 (1990)), was diluted into assay buffer (i.e., 50mM Tris, 50mM NaCl, 1mM EDTA, 1mM EGTA, and 5mM ß-mercaptoethanol, pH 7.5 including 0.2mM Succ-Leu-Tyr-MNA) and 175 µl aliquoted into the same wells containing the independent inhibitor stocks as well as to positive control wells containing 5 µl DMSO, but no compound. To start the reaction, 20) µl of 50 mM $CaCl_2$ in assay buffer was added to all wells of the plate, excepting three, which were used as background signal baseline controls. Substrate hydrolysis was monitored every 5 minutes for a total of 30 minutes. Substrate hydrolysis in the absence of inhibitor was linear for up to 15 minutes.

Inhibition of calpain I activity was calculated as the percent decrease in the rate of substrate hydrolysis in the presence of inhibitor (v_i) relative to the rate in its absence (v_o). Comparison between v_o and v_i was made within the linear range for substrate hydrolysis. For screening, compounds were tested at 10 µM. Compounds having 50% inhibition at 10 µM were considered active. Apparent second order rate constants were determined from analysis of reaction progress curves under pseudo-first order conditions. Each determination represents the mean of three or more independent single cuvette analyses continually monitored via a Perkin-Elmer LS50B spectrofluorimeter. The rate of inhibition of hydrolysis was obtained by fitting the curve to the exponential equation (1):

$$y = Ae^{-(k_{obs} * t)} + B \qquad (1)$$

In the above equation 1, y is P_t, which is the amount of product formed at time t; k_{obs} is the pseudo-first order rate constant for inactivation; A is a constant which is the amplitude of the reaction, given by $[P_o-P_\infty]$, which is the difference between the product formed at t=0 (P_o) and the maximal product formed when the reaction is complete (P_∞); B

is a constant which is the maximal product formeed when the reaction is complete (P_∞); k_{app} is the apparent ssecond order rate constant, determined as $k_{obs}/[I]$, where [I] iis inhibitor concentration. k_{app} was corrected for the presencce of substrate to give the second order rate constant: k_2 according to equation (2):

$$k_2 = k_{app} \ (1 + [S] \ / \ K_m) \qquad (2)$$

wherein [S] is substrate concentration, and K_m iss the Michaelis constant.

Values for k_{obs}/I are given in Table I.

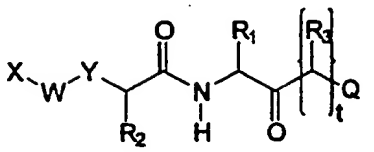


Table I

Ex. #	X-W-Y-	Q	t	k_{obs}/II x 10^{-3} $M^{-1}s^{-1}$	% Inhib. @ 0.1 uM
	R_1 = CH_2Ph; R_2 = iBu; R_3 = H				
34	$C_6H_5CH_2OCONH$	$OP(O)(OCH_2C_6H_5)_2$	1	1000	
35	$t-C_4H_9OCONH$	$OP(O)(OCH_2C_6H_5)_2$	1	2442	100
36	Morpholinyl sulfonyl-NH	$OP(O)(OCH_2C_6H_5)_2$	1	1882	
37	Diisopropylidine-2-keto-L-gulonyl-NH	$OP(O)(OCH_2C_6H_5)_2$	1	1113	
38	Monoisopropylidine-2-keto-L-gulonyl-NH	$OP(O)(OCH_2C_6H_5)_2$	1	1116	
39	$C_6H_5CH_2OCONH$	$OP(O)(OCH_2C_6H_4-2-CH_3)_2$	1	3665	
40	$C_6H_5CH_2OCONH$	$OP(O)(OCH_2C_6H_4-3-OC_6H_5)_2$	1		53
41	$t-C_4H_9OCONH$	$OP(O)(OH)_2$	1	<220	7
42	$C_6H_5CH_2OCONH$	$OP(O)(OCH_3)_2$	1	220	
43	$C_6H_5CH_2OCONH$	$OP(O)(OC_4H_9)_2$	1	440	
44	$C_6H_5CH_2OCONH$	$OP(O)(OCH_2CH(C_2H_5)C_4H_9)_2$	1	1	
45	$t-C_4H_9OCONH$	$OP(O)(OCH_2CH_2$-cyclohexyl$)_2$	1		28
46	$C_6H_5CH_2OCONH$	$OP(O)(OCH_2CH_2C_6H_5)_2$	1	3880	99
47	$C_6H_5CH_2OCONH$	$OP(O)(OCH_2)_2CHOCH_2C_6H_5$	1		47
48	$C_6H_5CH_2OCONH$	$OP(O)(CH_3)(OCH_2C_6H_5)$	1	<110	0
49	$C_6H_5CH_2OCONH$	$OP(O)(C_6H_5)(OCH_2C_6H_5)$	1	3337	90
50	$C_6H_5CH_2OCONH$	$OP(O)(C_6H_5)(OCH_2CH_2$-morpholine)	1	170	

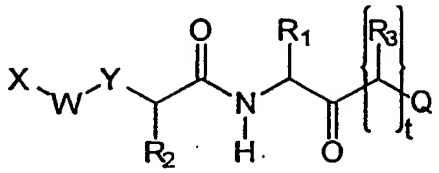
51	$C_6H_5CH_2OCONH$	OP(O)(C_6H_5)(OCH_2-CH_2-pyrrolidinone)	1	26	
52	$C_6H_5CH_2OCONH$	OP(O)(CH_3)$_2$	1	6	
53	$C_6H_5CH_2OCONH$	OP(O)(C_5H_{11})$_2$	1		19
54	$C_6H_5CH_2OCONH$	OP(O)($CH_2CH_2C_6H_5$)$_2$	1	8	15
55	$C_6H_5CH_2OCONH$	OP(O)(C_6H_4-2-CH_3)$_2$	1	31	
56	t-C_4H_9OCONH	OP(O)(C_6H_4-2-CH_3)$_2$	1	22	
57	$C_6H_5CH_2OCONH$	OP(O)(C_6H_4-4-OCH_3)$_2$	1	85	85
58	$C_6H_5CH_2OCONH$	OP(O)(C_6H_5)(C_6H_4-2-OCH_3)	1	150	
59	$C_6H_5CH_2OCONH$	OP(O)(C_6H_5)(C_6H_4-3-OCH_3)	1	163	
60	$C_6H_5CH_2OCONH$	OP(O)(C_6H_5)(C_2H_5)	1	6	51
61	$C_6H_5CH_2OCONH$	OP(O)(C_6H_5)(CH_2-CH_2CH_2-morpholine)	1	17	
62	$C_6H_5CH_2OCONH$	OP(O)(CH_2)$_2C_6H_4$	1		34
63	$C_6H_5CH_2OCONH$	OP(O)(CH_2CH=)$_2$	1		22
64	$C_6H_5CH_2OCONH$	P(O)(OC_2H_5)(C_6H_5)	1	4	26
65	$C_6H_5CH_2OCONH$	P(O)(OCH_3)(OH)	0		19
66	$C_6H_5CH_2OCONH$	P(O)(OC_4H_9)$_2$	0		0
67	$C_6H_5CH_2OCONH$	P(O)(OC_6H_5-4-Cl)$_2$	0		4
68	$C_6H_5CH_2OCONH$	P(O)(OC_2H_5)(C_6H_5)	0		0

It is intended that each of the patents, publications, and other published documents mentioned or referrred to in this specification be herein incorporated by refference in their entirety.

As those skilled in the art will appreciatee, numerous changes and modifications may be made to the preeferred embodiments of the invention without departing ffrom the spirit of the invention. It is intended that alll such variations fall within the scope of the inventicon.

WHAT IS CLAIMED IS:

1. A compound of the formula:



wherein:

X is selected from the group consisting of aaryl having from about 6 to about 14 carbons, heteroaryl haviing from about 6 to about 14 ring atoms, aralkyl having frrom about 7 to about 15 carbons, alkyl having from 1 to aboutt 10 carbons, said alkyl groups being optionally substtituted with one or more J groups, heteroalkyl having from 2 tto about 7 carbons, alkoxy having from 1 to about 10 carbonss, aralkyloxy having from about 7 to about 15 carbonns, and a carbohydrate moiety optionally containing one or more alkylated hydroxyl groups;

W is selected from the group consisting of ccarbonyl and SO_2;

Y is selected from the group consisting of NNH and $(CH_2)_k$ where k is an integer from 0 to 3;

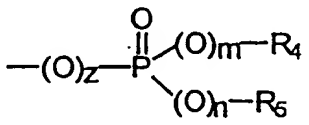
R_1 and R_2 are independently selected from thee group consisting of hydrogen, alkyl having from one to about 14 carbons, and cycloalkyl having from 3 to about 100 carbons, said alkyl and cycloalkyl groups being optionallyy substituted with one or more J groups;

R_3 is selected from the group consisting of hydrogen, lower alkyl, aryl, heteroaryl, aralkyl, and heterroaralkyl;

t is 0 or 1;

J is selected from the group consisting of halogen, alkyl, aryl, heteroaryl, amino optionally substituted with one to three aryl or lower alkyl groups, guanidino, alkoxycarbonyl, alkoxy, hydroxy, aryloxy, aralkyloxy, heteroalkyl, and carboxy; and

Q has the formula



wherein:

m, n, and z are each independently 0 or 1;

R_4 and R_5 are each independently selected from the group consisting of hydrogen, lower alkyl optionally substituted with J, aryl optionally substituted with J, aralkyl optionally substituted with J, and heteroaryl optionally substituted with J;

or R_4 and R_5 may be taken together along with the $-(O)_m-P(=O)-(O)_n-$ of Q to form a 5-8 membered heterocyclic ring optionally substituted with J;

or R_4 and R_5 may be taken together to form an aralkyl group;

with the proviso that when t is 0, z is also 0; and with the proviso that when m and n are both 0, and t and z are both 1, R_4 and R_5 cannot be unsubstituted phenyl or halogen-substituted phenyl; and with the further proviso that R_1 cannot be methylene substituted with carboxy.

2. A compound of claim 1 wherein z is 0.

3. A compound of claim 1 wherein z is 1.

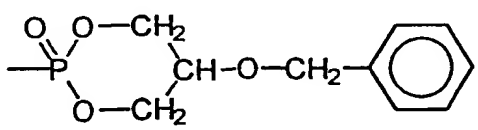
4. A compound of claim 1 wherein both m annd n are 1.

5. A compound of claim 4 wherein R_4 and R_5 are independently selected from the group consisting of hydrogen, lower alkyl optionally substituted withh J, aryl substituted with J, and aralkyl optionally substiituted with J; or R_4 and R_5 taken together along with the $-(O))_m-P(=O)-(O)_n-$ of Q form a six membered ring that is substiituted by J.

6. A compound of claim 5 wherein J is indeependently selected from the group consisting of alkyl, aryll, aryloxy, and halogen.

7. A compound of claim 6 wherein R_4 and R_5 are independently selected from the group consisting of hydrogen, lower alkyl, lower alkyl substituted wiith alkyl, lower alkyl substituted with aryl, aryl substitutted with halogen, aralkyl, aralkyl substituted with alkyl,, and aralkyl substituted with aryloxy, or R_4 and R_5 takken together along with the $-(O)_m-P(=O)-(O)_n-$ of Q form a six mmembered ring that is substituted by aralkyloxy.

8. A compound of claim 7 wherein R_4 and R_5 are independently selected from the group consisting of H, methyl, butyl, 2-ethylhexyl, 2-cyclohexylethyl, 22-phenylethyl, 4-chlorophenyl, benzyl, 2-methylbenzzyl, and 3-phenoxybenzyl, or R_4 and R_5 taken together along wwith the $-(O)_m-P(=O)-(O)_n-$ of Q form a six-membered ring havving the formula:



9. A compound of claim 8 wherein R_4 and $R_{5'5}$ are independently selected from the group consisting of benzyl, 2-methylbenzyl, and 2-phenylethyl.

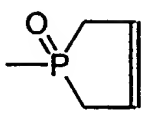
10. A compound of claim 1 wherein m and n are 0.

11. A compound of claim 10 wherein R_4 and R_5 are independently selected from the group consisting of lower alkyl optionally substituted with J, aralkyl, and aryl optionally substituted with J, or R_4 and R_5, taken together along with the $-(O)_m-P(=O)-(O)_n-$ of Q form a five membered ring.

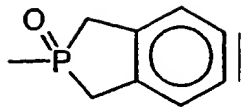
12. A compound of claim 11 wherein J is independently selected from the group consisting of alkyl, aryl, heteroalkyl, and alkoxy.

13. A compound of claim 12 wherein R_4 and R_5 are independently selected from the group consisting of lower alkyl optionally substituted with alkyl or aryl, lower alkyl substituted with heteroalkyl, aryl optionally substituted with alkyl or alkoxy, or R_4 and R_5, taken together along with the $-(O)_m-P(=O)-(O)_n-$ of Q form a five membered ring.

14. A compound of claim 13 wherein R_4 and R_5 are independently selected from the group consisting of methyl, ethyl, pentyl, 2-phenylethyl, phenyl, 2-methylphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, and 3-morpholinopropyl, or R_4 and R_5, taken together along with the $-(O)_m-P(=O)-(O)_n-$ of Q to form a five-membered ring having the formula:



or the formula



15. A compound of claim 1 wherein m is 1 annd n is 0.

16. A compound of claim 15 wherein R_4 and R_5 are independently selected from the group consisting of lower alkyl optionally substituted with J, aryl, and arralkyl.

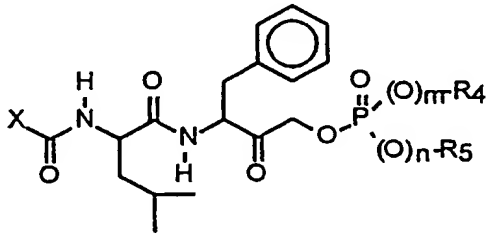
17. A compound of claim 16 wherein J is hetteroalkyl.

18. A compound of claim 17 wherein R_4 and R_5 are independently selected from the group consisting of methyl, ethyl, benzyl, phenyl, 2-morpholinoethyl, and 2-(2-oxopyrrolidin-1-yl)ethyl.

19. A compound of claim 1 wherein t is 1.

20. A compound of claim 1 wherein t is 0.

21. A compound of claim 1 having the formulla:



22. A compound of claim 21 wherein X is sellected from the group consisting of alkoxy having from 1 to about 10 carbons, aralkyloxy having from about 7 to about 15 carbons, and a carbohydrate moiety optionally containing cone or more alkylated hydroxyl groups.

23. A compound of claim 22 wherein X is sellected form the group consisting of benzyloxy, t-butoxy, diisopropylidine-2-keto-L-gulonyl, and monoisoprcopylidine-2-keto-L-gulonyl.

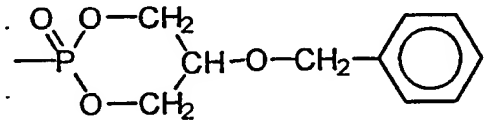
24. A compound of claim 21 wherein m and n are 1.

25. A compound of claim 24 wherein R_4 and R_5 are independently selected from the group consisting of hydrogen, lower alkyl optionally substituted with J, aryl substituted with J, and aralkyl optionally substituted with J; or R_4 and R_5 taken together along with the $-(O)_m-P(=O)-(O)_n-$ of Q form a six membered ring that is substituted by J.

26. A compound of claim 25 wherein J is independently selected from the group consisting of alkyl, aryl, aryloxy, and halogen.

27. A compound of claim 26 wherein R_4 and R_5 are independently selected from the group consisting of hydrogen, lower alkyl, lower alkyl substituted with alkyl, lower alkyl substituted with aryl, aryl substituted with halogen, aralkyl, aralkyl substituted with alkyl, and aralkyl substituted with aryloxy, or R_4 and R_5 taaken together along with the $-(O)_m-P(=O)-(O)_n-$ of Q form a six membered ring that is substituted by aralkyloxy.

28. A compound of claim 27 wherein R_4 and R_5 are independently selected from the group consisting of H, methyl, butyl, 2-ethylhexyl, 2-cyclohexylethyl, 22-phenylethyl, 4-chlorophenyl, benzyl, 2-methylbenzzyl, and 3-phenoxybenzyl, or R_4 and R_5 taken together along wwith the $-(O)_m-P(=O)-(O)_n-$ of Q form a six-membered ring heaving the formula:



29. A compound of claim 28 wherein R_4 and R_5 are independently selected from the group consisting of benzyl, 2-methylbenzyl, and 2-phenylethyl.

30. A compound of claim 21 wherein m and n are 0.

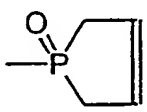
31. A compound of claim 30 wherein R_4 and R_5 are independently selected from the group consisting of lower alkyl optionally substituted with J, aralkyl, and aryl optionally substituted with J, or R_4 and R_5, taken together along with the $-(O)_m-P(=O)-(O)_n-$ of Q form a five membered ring.

32. A compound of claim 31 wherein J is independently selected from the group consisting of alkyl, aryl, heteroalkyl, and alkoxy.

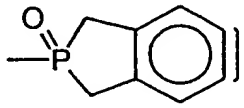
33. A compound of claim 32 wherein R_4 and R_5 are independently selected from the group consisting of lower alkyl optionally substituted with alkyl or aryl,, lower alkyl substituted with heteroalkyl, aryl optionally substituted

with alkyl or alkoxy, or R_4 and R_5, taken together along with the $-(O)_m-P(=O)-(O)_n-$ of Q form a five membered ring.

34. A compound of claim 33 wherein R_4 and R_5 are independently selected from the group consisting of methyl, ethyl, pentyl, 2-phenylethyl, phenyl, 2-methylpheenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, and 3-morpholinopropyl, or R_4 and R_5, are taken together along with the $-(O)_m-P(=O)-(O)_n-$ of Q to form a five-membereed ring having the formula:



or the formula



35. A compound of claim 21 wherein m is 1 and n is 0.

36. A compound of claim 35 wherein R_4 and R_5 are independently selected from the group consisting of lower alkyl optionally substituted with J, aryl, and aralkyl.

37. A compound of claim 36 wherein J is heteroalkyl.

38. A compound of claim 37 wherein R_4 and R_5 are independently selected from the group consisting of methyl, ethyl, benzyl, phenyl, 2-morpholinoethyl, and 2-(2-oxopyrrolidin-1-yl)ethyl.

39. A compound of claim 1 wherein t is 1; z is 1; J is selected from the group consisting of halogen, lower alkyl, aryl, heteroaryl, amino optionally substituted with one to three aryl or lower alkyl groups, guanidino, alkoxycarbonyl, alkoxy, hydroxy, and carboxy; and R_4 and R_5 are each

independently selected from the group consisting of hydrogen, lower alkyl optionally substituted with J, aryl optionally substituted with J, heteroaryl optionally substituted with J; or R_4 and R_5 may be taken together along with the $-(O)_m-P(=O)-(O)_n-$ of Q to form a 5-8 membered heterocyclic ring; or R_4 and R_5 may be taken togetther to form a 5-8 membered ring optionally substituted with JJ.

40. A compound of claim 1 wherein X is benzzyloxy; W is carbonyl; Y is NH; R_1 is benzyl; R_2 is isobutyl; R_3 is hydrogen; t, z, m, and n are each 1; and R_4 and R_5 are each 2-methylbenzyl.

41. A compound of claim 1 wherein X is benzzyloxy; W is carbonyl; Y is NH; R_1 is benzyl; R_2 is isobutyl; R_3 is hydrogen; t, z, m, and n are each 1; and R_4 and R_5 are each 2-phenylethyl.

42. A compound of claim 1 wherein X is benzzyloxy; W is carbonyl; Y is NH; R_1 is benzyl; R_2 is isobutyl; R_3 is hydrogen; t, z, are each 1; m is 1; n is 0; R_4 is benzyl; and R_5 is phenyl.

43. A composition for inhibiting a protease selected from the group consisting of serine proteases and cysteine proteases comprising a compound of claim 1.

44. A method for inhibiting a protease comprising contacting a protease selected from the group consisting of serine proteases and cysteine proteases with an inhibitory amount of a compound of claim 1.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/116625

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :Please See Extra Sheet.
US CL :514/42, 90, 91, 105, 119; 536/29.1; 544/157; 548/413; 558/83, 172
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/42, 90, 91, 105, 119; 536/29.1; 544/157; 548/413; 558/83, 172

Documentation searched other than minimum documentation to the extent that such documents are includedd in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicablele, search terms used)

CAS ONLINE, Registry Database, structure-based search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Database CAPLUS on STN, Chemical Abstracts Service, (Columbus, OH), Accession No. 1988:611439, SCHLEMMER, H. ET AL., "Phosphorus-31 Nuclear Magnetic Resonance Spectroscopy of the Phosphorylated Tetrapeptide Gly-Gly-Asp-Ala", Magn. Reson. Chem. (1988), 26(3), 260-3, abstract. Note compound with registry no. 117289-76-6.	1, 3-8, 20
X	Database CAPLUS on STN, Chemical Abstracts Service, (Columbus, OH), Accession No. 1995:297974, DOLLE, R.E. ET AL., "Aspartyl α-((Diphenylphosphinyl)oxy)methylKetones as Novel Inhibitors of Interleukin-1β Converting Enzyme. Utility of the Diphenylphosphonic Acid Leaving Group for the Inhibition of Cysteine Proteases", J. Med. Chem. (1995), 38(2), 220-2, abstract.	1, 3, 10-15, 19, 21-23, 30-34, 39, 43, 44

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the inteternational filing date or priority date and not in conflict with the applicicatiion but cited to understand the principle or theory underlying the invevention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; thdhe claimed invention cannot be considered novel or cannot be considelered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; thdhe claimed invention cannot be considered to involve an inventive:e step when the document is combined with one or more other suchch documents, such combination being obvious to a person skilled in thdhe art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent it family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 16 SEPTEMBER 1996	Date of mailing of the international seaarch report 02 OCT 1996
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer MICHAEL G. AMBROSE Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/11625

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Database CAPLUS on STN, Chemical Abstracts Service, (Columbus, OH), Accession No. 1995:867576, STERLING-WINTHROP, INC. "Preparation of Peptide Derivatives as Interleukin 1β-converting Enzyme Inhibitors", JP 07025887 A2. Jpn. Kokai Tokkyo Koho. 27 January 1995, abstract. Note listing of disclosed compounds.	1, 3, 10-14, 19, 39
X	Database CAPLUS on STN, Chemical Abstracts Service, (Columbus, OH), Accession No. 1984:51966, RAMAGE, R. ET AL., "Application of Phosphinic Acids to Peptide Synthesis", Pept. Proc. Eur. Pept. Symp., 17th (1983), Meeting Date 1982, 157-62, abstract. Note compound with registry no. 88577-10-0.	1, 3, 10-14, 19, 39

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/116625

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6):

A61K 31/66, 31/665, 31/675; C07F 9/09, 9/32, 9/40, 9/53, 9/572, 9/6533, 9/6574